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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/522,944

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Wayne R. Danter

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EXAMINER

RAO, DEEPAK R

ART UNIT

PAPER NUMBER

1624

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,944	DANTER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>20050131, 20051205, 20060206, 20060329 & 20060814</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-25 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-10, 15-23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a compound of formula I; or a method of treating cancers of the breast, colon, prostate, and ovary; or a method of treating melanoma or chronic myeloid leukemia (CML), does not reasonably provide enablement for a compound that inhibits, regulates and/or modulates tyrosine kinase signal transduction generally; or a method of treating or **preventing** a tyrosine kinase-dependent disease or condition generally; or a composition comprising the compound of formula I and a compound selected from the group consisting of estrogen receptor modulator, an MMP inhibitor, ... thalidomide, ...raloxifene (claim 25). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples,

6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Claims 9-10 recite “the compound inhibits, regulates and/or modulates tyrosine kinase signal transduction”. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

It is generally known that the terms “modulate” or “regulate” encompasses agonism, antagonism, partial antagonism and partial agonism. However, the claimed compounds were not shown to have all these properties. The specification only provides *in vitro* anticancer data in specific cancer cell types and there is no disclosure, how one of ordinary skill in the art can extrapolate this data to find the 'inhibition, regulation or modulation of tyrosine kinase signal transduction' activity of the compounds. For example, it is revolutionary for a compound to be effective as an agonist/antagonist and partial agonist/antagonist. The specification did not provide any competent tests or data to establish that the compounds have the claimed 'tyrosine kinase inhibiting, regulating and/or modulating activity'.

The instant claim 25 is drawn to 'a composition comprising a compound of formula I and additionally a second compound' and the specification at pages 23-26 provides some explanation of the 'second compound' intended by the claim, however, the scope of the claim includes

therapeutic agents that are known and those that may be discovered in future, for which there is no enablement. Further, the entire scope of the therapeutic activity intended for the compounds of the invention is not enabled for the reasons provided below.

The instant claims 15-23 are drawn to 'a method for treating or **preventing** a tyrosine kinase-dependent disease or condition'. The example in page 28 of the specification provides *in vitro* anticancer data for the exemplified compounds against specific cancer cell types. The instant claims, however, appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays provided in the specification at page 28 are related to specific cancer cells, however, there is no disclosure regarding how this data is extrapolated to the treatment and **prevention** of the all types of diseases and conditions encompassed by the instant claims. Applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification page 27, the activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the kinases.

The instant claims 15-23 are drawn to "a method for treating or **preventing** a tyrosine kinase-dependent disease or condition". The use disclosed in the specification is as SYK and ZAP-70 kinase inhibitors, useful to treat a large list of diverse diseases, some of which are listed

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in page 11. Example 1 in page 28 of the specification describes the anti-cancer activity of some of the compounds in specific cell types, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of proliferative disorders, cancers, tumors, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms.

For example, the instant claims are drawn to 'treating or **preventing** various types of cancers' which includes treatment of all types of cancers of blood, lymphocytes, etc. A 'cancer' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers,

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but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “silver bullet” is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study” (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein ‘evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers’. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that “pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles” see page 585, col. 2, lines 33-36.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in

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general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that “The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.”, see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

Further, the instant claims are drawn not only to 'a method of treating' but also to '**a method of preventing**', for which the specification does not provide sufficient enablement. 'To prevent' actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the recited effect of **prevention**. Based on the inhibitory activity, the instant compounds are disclosed to be useful in the “prevention” of, for example, degenerative disorders, for which applicants provide no competent evidence. It is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the “treating or **preventing**” of the various claimed disorders, such that the claimed compounds can not only treat but also “prevent” a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of “preventing”. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex*

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parte Stevens, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as “showing” such utility, and not “warranting further study”).

Part of the difficulty of developing drugs effective for **preventing** any of the medical conditions such as cancers, tumors, etc. lies in the lack of understanding as to why people come down with these disorders and the numerous causes of these disorders.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. In claim 1, it is not clear what number range is intended by the definition provided for “ n ”. It is recited that “n is an integer”, however, there is no value provided.

Duplicate Claims

1. Applicant is advised that should claim 1 be found allowable, claims 9-10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 9-10 provide a characteristic of the compound of claim 1 and do not further limit the scope of claim 1.
2. Applicant is advised that should claim 11 be found allowable, claim 24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 11 and 24 are of the same scope as both the claims comprise the compound and a pharmaceutically acceptable carrier.

Receipt is acknowledged of the Information Disclosure Statements filed on January 31, 2005; December 5, 2005; February 6, 2006; March 29, 2006 and August 14, 2006 and copies are enclosed herewith. The IDS filed on December 5, 2005 lists numerous U.S. and Foreign patent documents for which there is no publication date provided on the PTO-1449 form which is

required. 37 CFR 1.98. The references have been crossed off from in PTO-1449 form and have not been considered at this time and the IDS does not meet the requirements of 37 CFR 1.98.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**/Deepak Rao/
Primary Examiner
Art Unit 1624**

April 22, 2008